REMARKS

Applicants respectfully request entry of the amendment and reconsideration of the claims. Claims 1, 18, and 24 have been amended. Claims 3-12 and 19 have been cancelled without prejudice or disclaimer. Claims 26-30 are newly presented. After entry of the amendment, claims 1-2, 18, and 24-30 will be pending.

Applicants submit the amendment places the claims in condition for allowance. The amendment is supported throughout the specification, including for example at page 2, lines 10-16, page 15, lines 3-6, 10-14 and 24-26, page 17, line 19 and the claims as originally filed, and does not introduce new matter.

35 U.S.C. § 103

Claims 1-13, 18-19, and 24-25 were rejected under 35 U.S.C. §103(a) as being obvious over Tsuji (U.S. 7,273,852) in view of Defrees (U.S. 5,604,207), Sinay (Bioorganic and Medicinal Chemistry, 6:1337-46 (1998)) and Kawano (Science, 278:1626-29 (1997)). Applicants respectfully traverse the rejection.

Without acquiescing to the rejection and solely for the purpose of advancing prosecution, claims 1 and 24 have been amended to recite that R_2, R_3, R_4, R_6, and R_7 are hydrogen and R_1 is $-C(O)R_{10}$, wherein R_{10} is C_1-C_{12} alkyl optionally substituted with a carboxyl. Applicants reserve the right to pursue the cancelled subject matter in a continuation application.

In order to establish a *prima facie* case of obviousness, it remains necessary for the Patent Office to establish some reason to arrive at the claimed compounds based on the prior art or general knowledge of those of skill in the art. While the Supreme Court in *KSR* rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 at 1731 (2007). Since *KSR*, the Federal Circuit has applied the obviousness test to chemical compounds, and has held that "in cases involving new chemical compounds, it remains

necessary to identify some reason that would lead a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." *Takeda Chemical Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007). The Board of Patent Appeals and Interferences also recognizes that examiners must identify a reason to make a claimed invention, even in the presence of related art, lest the examiners fall prey to the "unwitting application of hindsight." *Ex parte Joseph K. So*, B.P.A.I. 2007-3967, at 5.

Applicants submit that the Office Action has failed to make the required *prima facie* case, as the cited references, either alone or in combination, do not teach or suggest all the limitations of the claims as amended and do not establish that one of skill in the art in view of the cited combination of references had a reasonable expectation of successfully arriving at the claims as amended.

The Office Action alleges obviousness based on similarity of structure and function entails motivation to make the claimed compounds in expectation that compounds similar in structure will have similar properties. Applicants respectfully assert that this characterization of the law of obviousness with respect to chemical compounds is incomplete and fails to account for recent applicable authority.

In addition to structural similarity between the compounds, a showing of "adequate support in the prior art" for the change in structure is also required. *Takeda Chemical Indus., Ltd v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007). A showing that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed compounds is required to establish a *prima facie* case of obviousness. *Id.* (emphasis added). Applicants submit the cited combination of references fails to teach or suggest the specific molecular modifications necessary to achieve the claimed compounds.

As discussed above, the claims have been amended to recite that R_1 is $-C(O)R_{10}$, wherein R_{10} is C_1-C_{12} alkyl optionally substituted with a carboxyl. Tsuji discloses a hydrogen or monosaccharide at the position corresponding to R_1. Neither Tsuji nor any of the cited secondary references teach or suggest a C_1-C_{12} alkyl at the position corresponding to R_1 or an amide at the C-6 position. The cited combination of references therefore fails to teach or suggest all the elements of the claims as amended.

Moreover, to derive the claimed compounds from those taught in Tsuji, a person of skill in the art would also be required to modify the Tsuji compounds by replacing the C-linkage at the glycosidic bond with an O-linkage. However, this particular modification is expressly disparaged by Tsuji. With respect to the O-linked compound "α-GalCer," Tsuji teaches:

> [M]ost mammals, including humans, have abundant amounts of α-galactosidase, an enzyme which digests α-GalCer by catalyzing the degradation of α-D-galactoside bonds. As a result, α-GalCer has a short-half life, and therefore its *in vivo* therapeutic effect may be reduced." (Col. 5, lines 40-45).

Tsuji teaches that C-linked compounds have "improved stability" and "improved therapeutic efficacy" over alpha-GalCer (Col. 5, lines 50-53) and are 100 to 1000 times more potent than the corresponding O-linked analogs (Col. 10, lines 5-17).

It is well established that "a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." MPEP § 2141.02 citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983) *cert. denied*, 469 U.S. 851 (1984). Given the teachings of Tsuji, one of skill in the art seeking to develop compounds for use in this field would not be motivated to use an O-linked glycolipid as a starting compound for further development as the O-linked glycolipid exhibited negative properties that would have directed one of ordinary skill in the art away from an O-linked glycolipid as a starting compound. Thus, Tsuji et al. teaches away from the use of an O-linkage in developing synthetic compounds in the field of the invention. *See Eli Lilly and Company v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369 (Fed. Cir. 2006) (holding claimed compound non-obvious despite description of close structural analog in prior art reference because that reference also expressed a strong preference for using a different substituent at another position) and *Takeda Chemical Indus., Ltd v. Alphapharm Pty., Ltd.*, 492 F.3d 1350(Fed. Cir. 2007) (holding one of skill in the art would not have selected compound b as the lead compound to modify to obtain a compound with better activity as compound b exhibited negative properties that would have directed one of ordinary skill in the art away from using compound b as the lead compound for modification).

The secondary Kawano reference fails to cure the deficiencies of the primary Tsuji reference. Kawano does not teach or suggest teach or suggest a C_1-C_{12} alkyl at the position corresponding to R_1 or an amide at the C-6 position.

Moreover, it is improper to combine references where the references teach way from their combination. MPEP § 2145(X)(D)(2) citing *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983). Kawano discuss various properties of the same O-linked compounds, and modifications of these compounds (all of which have an O-linkage), that Tsuji disparages. Thus, there is simply no teaching in either reference that the compounds should be modified or combined in any particular manner to arrive at the claimed compounds as the Tsuji and Kawano references teach away from their combination. *See Alza Corp. v. Mylan Labs., Inc.*, 391 F.3d 1365, 1373 (Fed. Cir. 2004) (holding method of using fentanyl base transdermally was non-obvious because reference that taught away from the transdermal use of fentanyl would not be combined by one of skill in the art with reference describing fentanyl base.)

When the prior art provides no motivation to make the claimed compounds, references which teach the formation of similar compounds cannot, alone, render the claimed compounds obvious. See *In re Stemniski*, 444 F.2d 581, 586 (C.C.P.A. 1971), affirmed in *In re Dillon*, 919 F.2d 688, 692-93 (Fed. Cir. 1990). Given that the Tsuji and Kawano references provide no motivation to make the claimed compounds for the reason discussed herein, the synthetic methods disclosed in Defrees and Sinay are not relevant to whether the claimed compounds are obvious.

The Kawano reference teaches that *only certain glycolipids* stimulate proliferation of $V_\alpha 14$ NKT cells, a class of cells suspected to play an important role in IL-12-mediated rejection of tumors. (*See* Kawano at 1628.) While Kawano suspected that glycolipids were important because of the association of CD1 molecules, Kawano noted a wide variety of $V_\alpha 14$ NKT cell responses due only to small changes in the structure of the glycolipids. (*See* Kawano at 1627.) For example α-GalCer (found in marine sponges) showed the greatest proliferative response, but α-ManCer, differing only in the configuration of the 2-hydroxyl bond, showed no stimulatory activity. (Kawano at 1627.) On the other hand, α-GlyCer, differing from α-GalCer only in the configuration of the 4-hydroxyl bond, showed identical stimulatory activity.

(Kawano at 1627.) Thus, Kawano teaches that activity of α-GlyCer compounds cannot be predicted from structure.

Even if there were motivation to develop the claimed compounds (which the Office Action has failed to establish for the reasons discussed herein and in the response filed July 8, 2008), one of skill in the art would not have had a reasonable expectation at successfully arriving at the claimed compounds as one of skill in the art of making and testing compounds in the same class as that of the claimed invention is aware that slight structural changes can have a dramatic effect on *in vitro* and *in vivo* efficacy. This unpredictability in the art is clearly illustrated by Kawano.

When the core structural features of a compound have interesting biological activity, the Office Action alleges structural modifications within the core to generate new derivatives with enhanced activity is routine in medicinal chemistry. Citing the Kawano reference for support, the Office Action alleges in structure-activity studies one of ordinary skill in that art would expect some compounds to show reduced activity and this is motivation keep looking for other similar compounds that show enhanced activity. Applicants respectfully do not agree.

"[T]o have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *Medichem v. Rolabo*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) *affirmed in Pfizer v. Apotex*, 480 F.3d 1348 (Fed. Cir. 2007). A showing that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed compounds is required. *Takeda*, 492 F.3d at 1356. For the reasons discussed above, the Office Action has failed to establish that the cited combination of references teaches or suggests the specific molecular modifications necessary to achieve the claimed compounds.

Moreover, Kawano teaches that activity of α-GlyCer compounds cannot be predicted from structure. The Kawano reference teaches that *only certain glycolipids* stimulate proliferation of $V_{\alpha}14$ NKT cells, a class of cells suspected to play an important role in IL-12-mediated rejection of tumors. (*See* Kawano at 1628.) While Kawano suspected that glycolipids

were important because of the association of CD1 molecules, Kawano noted a wide variety of $V_{\alpha}14$ NKT cell responses due only to small changes in the structure of the glycolipids. (*See* Kawano at 1627.) Because one of skill in the art cannot reasonably predict whether or not a given glycolipid will stimulate NKT activity, there cannot be a reasonable expectation of success based upon the prior art alone. Therefore, absent Applicants' disclosure, one of skill in the art would not have been motivated to make the claimed compounds or reasonably expected that the claimed compounds would stimulate NKT activity.

Citing column 3, lines 55-60 of the Tsuji reference, the Office Action alleges Tsuji suggests substituted amino sugar moieties and that it would have been obvious to move the substituted amino sugar moiety at the C-2 position to the C-6 position to determine its activity as part of an optimization/structure-activity study. Applicants respectfully do not agree.

Applicants submit it would not have been obvious to one of skill in the art to move a substituent at the C-2 position to the C-6 position as the C-6 position is not a ring carbon and none of the cited references, alone or in combination, teach or suggest that a substituent at the C-6 position (which is outside of the ring) is functionally equivalent or analogous to the same substituent at the C-2 position (which is a cyclic carbon) or would result in beneficial changes to the activity of the compound. *See Takeda Chemical Indus., Ltd v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007) (No reasonable expectation in the art that changing the positions of a substituent on a pyridyl ring would result in beneficial changes).

As the Office Action has failed to establish that the claimed compounds are *prima facie* obviousness over the cited combination of references, claim 18 which recites a method of stimulating NKT cells with the claimed compounds and claim 24 which recites a method for making the claimed compounds are also not *prima facie* obviousness for the reasons discussed above.

In view of the forging, Applicants submit the Office Action has failed to establish a *prima facie* case of obviousness. The cited combination of references fails to teach or suggest all the elements of the claims as amended. In addition, the cited combination of references teaches away from the claimed compounds and fails to establish that one of skill in the art would have been motivated to make the claimed compounds or had a reasonable expectation

that the claimed compounds would stimulate NKT activity. Withdrawal of the rejection is therefore respectfully requested.

Conclusion

In view of the above amendment and remarks, Applicants submit the claims are in condition for allowance and a Notice of Allowance to that effect is respectfully requested. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(612) 332-5300

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Eric E. DeMaster
Reg. No. 55,107

Wendy M. Ward
Reg. No. 52,205
WMW:EED:jrm